

Amendments to the Specification:

Please insert the Sequence Listing being filed concurrently herewith into the specification.

Please amend paragraph 43 on page 17 as follows.

To better understand the higher RNA affinity of 2'-*O*-methoxyethyl substituted RNA and to examine the conformational properties of the 2'-*O*-methoxyethyl substituent, two dodecamer oligonucleotides were synthesized having SEQ ID NO: [1] 7 (CGC GAA UUC GCG) and SEQ ID NO: [2] 8 (GCG CUU AAG CGC). These self-complementary strands have every 2'-position modified with a 2'-*O*-methoxyethyl. The duplex was crystallized at a resolution of 1.7 Ångstrom and the crystal structure was determined. The conditions used for the crystallization were 2 mM oligonucleotide, 50 mM Na Hepes pH 6.2-7.5, 10.50 mM MgCl₂, 15% PEG 400. The crystal data showed: space group C2, cell constants *a*=41.2 Å, *b*=34.4 Å, *c*=46.6 Å, α =92.4°. The resolution was 1.7 Å at -170°C. The current *R*=factor was 20% (*R*_{free} 26%).

Please amend paragraph 80 spanning pages 38-40 as shown below.

RNAi and other compounds of the invention which hybridize to the target and inhibit expression of the target are identified through experimentation, and the sequences of these compounds are hereinbelow identified as preferred embodiments of the invention. The target sites to which these preferred sequences are complementary are hereinbelow referred to as "active sites" and are therefore preferred sites for targeting. Therefore another embodiment of the invention encompasses compounds, including primers, probes, siRNAs, other double stranded RNAs including RNAi or gene silencing agents, ribozymes, external guide sequence (EGS) oligonucleotides (oligozymes), and other short catalytic RNAs or catalytic oligonucleotides which hybridize to these active sites.

Some representative siRNA oligomers as per the invention include:

Sequence	SEQ ID NO.	Features
----------	---------------	----------

5'-CCU UUU UGU CUC UGG UCC UU-3'	[3] <u>9</u> 5'-phosphate, 3'-OH, all PO
5'-CCU UUU UGU CUC UGG UCC UU-3'	[3] <u>9</u> 5'-phosphate, 3'-OH, all PS
5'-CCU UUU UGU CUC UGG UCC UU-3'	[3] <u>9</u> 5'-thiophosphate, 3'-OH, all PS
5'-CCU UUU UGU CUC UGG UCC UU-3'	[3] <u>9</u> 5'-phosphate, 3'-OH, all F/ PO
5'-CCU UUU UGU CUC UGG UCC UU-3'	[3] <u>9</u> 5'-phosphate, 3'-OH, all F/PS
5'-CCU UUU UGU CUC UGG UCC <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F, all PS
5'-CCU UUU UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F, all PS
5'-CCU UUU UGU CUC <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F, all PS
5'-CCU UUU UGU CUC <u>UGG</u> UCC <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F / all PS
5'-CCU UUU UGU CUC <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-thiophosphate, 3'-OH, F / all PS
5'- <u>CCU</u> UUU UGU CUC UGG UCC <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F, all PS
5'- <u>CCU</u> UUU UGU CUC UGG UCC <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'- OH, F, all PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'- OH, F, all PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'- OH, F, all PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'- OH, F, all PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'- OH, F, all PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F, P _O , rest PS
5'-CCU UUU UGU CUC UGG UCC <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, OMe, PS
5'-CCU UUU UGU CUC UGG UCC <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, OMe, PS
5'-CCU UUU UGU CUC UGG UCC <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, OMe, PS
5'-CCU UUU UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, OMe, PS
5'-CCU UUU UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, OMe, PS
5'-CCU UUU UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, OMe, PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG UCC <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F, OMe, PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG UCC <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F, OMe, PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[4] <u>10</u> 5'-phosphate, 3'-OH, F, OMe, PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F, OMe, PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F, P _O , OMe, rest PS
5'- <u>CCU</u> <u>UUU</u> UGU CUC UGG <u>UCC</u> <u>UU</u> -3'	[3] <u>9</u> 5'-phosphate, 3'-OH, F, P _O , OMe, rest PS

5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>F</u> , <u>deoxy</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>F</u> , <u>deoxy</u> , PO
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>F</u> , <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>F</u> , <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>F</u> , <u>LNA</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA/PO</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA/PO</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA/PO</u> , PS
5'- <u>CCU</u> <u>UUU</u> <u>UGU</u> <u>CUC</u> <u>UGG</u> <u>UCC</u> <u>UU</u> -3'	[3] <u>2</u> 5'-phosphate, 3'-OH, <u>LNA/PO</u> , PS

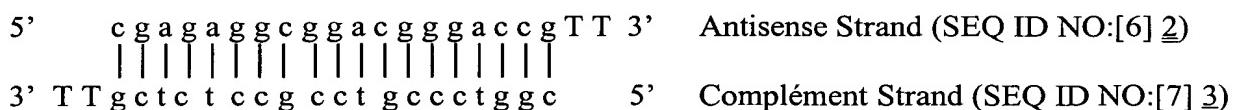
Definitions:

PS =	phosphorothioate internucleotide linkage
PO =	phosphodiester internucleotide linkage
PO =	phosphodiester internucleotide linkage
<u>deoxy</u> =	2'-deoxy nucleotide
<u>F</u> =	2'-fluoro
3'-OH =	3'-terminus has a hydroxyl group
OMe =	2'-O-methyl
<u>LNA</u> =	locked nucleic acid
<u>LNA/PO</u> =	LNA with phosphodiester internucleotide linkages
5'-phosphate =	5'-terminus has a phosphate group

Note: Each nucleoside marked to indicate a specific linkage type indicates that the particular linkage (e.g. PO or PS) is attached to the 5'-position of that nucleoside completing the internucleoside linkage by making a second attachment to an adjacent nucleoside at its 3'-position.

Please amend paragraph 252 at page 99 as follows.

For example, a duplex comprising an antisense strand having the sequence CGAGAGGCGGACGGGACCG (SEQ ID NO: [5] 1) and having a two-nucleobase overhang of deoxythymidine(dT) would have the following structure:



Please amend paragraph 267 spanning pages 103-104 as shown below.

The concentration of oligonucleotide used varies from cell line to cell line. To determine the optimal oligonucleotide concentration for a particular cell line, the cells are treated with a positive control oligonucleotide at a range of concentrations. For human cells the positive control oligonucleotide is selected from either ISIS 13920 (**TCCGTCATCGCTCCTCAGGG**, SEQ ID NO: [5] 4) which is targeted to human H-ras, or ISIS 18078, (**GTGCGCGCGAGCCCCGAAATC**, SEQ ID NO: [6] 5) which is targeted to human Jun-N-terminal kinase-2 (JNK2). Both controls are 2'-O-methoxyethyl gapmers (2'-O-methoxyethyls shown in bold) with a phosphorothioate backbone. For mouse or rat cells the positive control oligonucleotide is ISIS 15770, **ATGCATTCTGCCCAAGGA**, SEQ ID NO: [7] 6, a 2'-O-methoxyethyl gapmer (2'-O-methoxyethyls shown in bold) with a phosphorothioate backbone which is targeted to both mouse and rat c-raf. The concentration of positive control oligonucleotide that results in 80% inhibition of c-H-ras (for ISIS 13920), JNK2 (for ISIS 18078) or c-raf (for ISIS 15770) mRNA is then utilized as the screening concentration for new oligonucleotides in subsequent experiments for that cell line. If 80% inhibition is not achieved, the lowest concentration of positive control oligonucleotide that results in 60% inhibition of c-H-ras, JNK2 or c-raf mRNA is then utilized as the oligonucleotide screening concentration in subsequent experiments for that cell line. If 60% inhibition is not achieved, that particular cell line is deemed as unsuitable for oligonucleotide transfection experiments. The concentrations of antisense oligonucleotides used herein are from 50 nM to 300 nM.

Please amend paragraph 295 on page 113 as follows.

The antisense (AS) strands listed below having SEQ ID NO: 9 were individually duplexed with the sense (S) strand having SEQ ID NO: 8 and the activity was measured to determine the relative positional effect of the 5 modifications.

<u>SEQ ID NO:/ISIS NO</u>	<u>Sequence</u>
[8] <u>11</u> /271790 (S)	5'-CAAAUCCAGAGGCUAGCAG-dTdT-3'
[9] <u>12</u> /271071(AS)	3'-dTdT-GUUUAGGUCUCC <u>GAUCGUC</u> -5'
[9] <u>13</u> /271072(AS)	3'-dTdT-GUUUAGGUCUCC <u>GAUCGUC</u> -5'
[9] <u>14</u> /271073(AS)	3'-dTdT-GUUUAGGUCUCC <u>GAUCGUC</u> -5'
[9] <u>15</u> /271074(AS)	3'-dTdT-GUUUAGGUCUCC <u>GAUCGUC</u> -5'
[9] <u>16</u> /271075(AS)	3'-dTdT-GUUUAGGUCUCC <u>GAUCGUC</u> -5'

Please amend paragraph 298 spanning pages 113-114 as shown below.

The antisense strands listed below having SEQ ID NO:9 were individually duplexed with the sense strand having SEQ ID NO:7 and the activity was measured to determine the relative effect of adding either 9 or 14, 2'-O-methyl modified nucleosides at the 3'-end of the resulting siRNA's.

<u>SEQ ID NO:/ISIS NO</u>	<u>Sequence</u>
[8] <u>11</u> /271790 (S)	5'-CAAAUCCAGAGGCUAGCAG-dTdT-3'
[10] <u>17</u> /271079(AS)	3'- <u>UUGUUUAGGUCUCCGAUCGUC</u> -5'
[10] <u>18</u> /271081(AS)	3'- <u>UUGUUUAGGUCUCCGAUCGUC</u> -5'

Please amend paragraph 301 on page 114 as follows.

A series of blockmers were prepared as duplexed siRNA's and also as single strand asRNA's. The antisense strands were identical for the siRNA's and the asRNA's.

<u>SEQ ID NO:/ISIS NO</u>	<u>Sequence 5'-3'</u>
[11] <u>19</u> /308746 (S)	5'-AAGUAAGGACCAGAGACAAA-3' (PO)
[12] <u>20</u> /303912 (AS)	3'-UUCAUUCUGGUCCUCUGUUU-P 5' (PS)
[12] <u>21</u> /316449 (AS)	3'- <u>UUCAUUCUGGUCCUCUGUUU-P</u> 5' (PS)
[12] <u>22</u> /335223 (AS)	3'-UUCAUUC <u>UGGUCCUCUGUUU-P</u> 5' (PS)
[12] <u>23</u> /335224 (AS)	3'-UUCAUUC <u>UGGUCCUCUGUUU-P</u> 5' (PS)
[12] <u>24</u> /335225 (AS)	3'-UUCAUUC <u>UGGUCCUCUGUUU-P</u> 5' (PS)
[12] <u>25</u> /335226 (AS)	3'-UUCAUUC <u>UGGUCCUCUGUUU-P</u> 5' (PS)
[12] <u>26</u> /335227 (AS)	3'-UUCAUUC <u>UGGUCCUCUGUUU-P</u> 5' (PS)
[12] <u>27</u> /335228 (AS)	3'-UUCAUUC <u>UGGUCCUCUGUUU-P</u> 5' (PS)

Please amend paragraph 302 spanning pages 114-115 as shown below.

Underlined nucleosides are 2'-O-methyl modified nucleosides, all other nucleosides are ribonucleosides and all internucleoside linkages for the AS strands are phosphorothioate and the internucleoside linkages for the S strand are phosphodiester.

SEQ ID NO: Sequence (5'-3')

- [11] 19 AAGUAAGGACCAGAGACAAA
[12] 20 UUUGUCUCUGGUCCUUACUU

Please amend paragraph 304 on page 115 as follows.

Blunt and overhanging siRNA constructs were prepared having a block of 5, 2'-O-methyl nucleosides at the 3'-terminus.

<u>SEQ ID NO:/ISIS NO</u>	<u>Sequence (overhangs)</u>
[8] <u>11</u> /271790 (S)	5'-CAAAUCCAGAGGCUAGCAG-dTdT-3'
[10] <u>28</u> /xxxxxx (AS)	3'-UUGUUUAGGUCUCCGA <u>UCGUC</u> -5'

<u>SEQ ID NO:/ISIS NO</u>	<u>Sequence (blunt)</u>
[13] <u>29</u> /xxxxx(S)	5'-GUCAAAUCCAGAGGCUAGCAG-3'
[14] <u>30</u> /xxxxxx (AS)	3'-CAGUUUAGGUCUCCGA <u>UCGUC</u> -5'

Please amend paragraph 305 spanning pages 115-116 as shown below.

Underlined nucleosides are 2'-O-methyl modified nucleosides, all other nucleosides are ribonucleosides and all internucleoside linkages for the AS strands are phosphorothioate and the internucleoside linkages for the S strand are phosphodiester.

SEQ ID NO: Sequence (5'-3')

[13] <u>29</u>	GUCAAAUCCAGAGGCUAGCAG
[14] <u>31</u>	CUGCUAGCCUCUGGAUUUGAC

Please amend paragraph 307 on page 116 as follows.

Three siRNA hemimer constructs were prepared and examined in a PTEN assay. The hemimer constructs had 7, 2'-O-methyl nucleosides at the 3'-end. The hemimer was put in the sense strand only, the antisense strand only and in both strands to compare the effects.

<u>SEQ ID NO:/ISIS NO</u>	<u>Constructs (overhangs)</u>
[15] <u>32</u> /271068 (S)	5'-CAAAUCCAGAGGCU <u>AGCAGUU</u> -3'
[10] <u>33</u> / (AS)	3'- <u>UUGUUUAGGUCUCCGAUCGUC</u> -5'
[15] <u>32</u> /271068 (S)	5'-CAAAUCCAGAGGCU <u>AGCAGUU</u> -3'
[10] <u>34</u> / (AS)	3'-UUGUUUAGGUCUCCGAUCGUC-5'
[15] <u>35</u> / (S)	5'-CAAAUCCAGAGGCU <u>AGCAGUU</u> -3'
[10] <u>33</u> / AS)	3'- <u>UUGUUUAGGUCUCCGAUCGUC</u> -5'

Please amend paragraph 308 on page 116 as shown below.

Underlined nucleosides are 2'-O-methyl modified nucleosides, all other nucleosides are ribonucleosides and all internucleoside linkages for the AS strands are phosphorothioate and the internucleoside linkages for the S strand are phosphodiester.

SEQ ID NO: **Sequence (5'-3')**

[15] 35 CAAAUCCAGAGGUAGCAGUU

Please amend paragraph 310 on page 117 as follows.

Four hemimers were prepared and assayed as the asRNA's and also as the siRNA's in a PTEN assay. The unmodified sequence was also tested as the asRNA and as the siRNA.

<u>SEQ ID NO:/ISIS NO</u>	<u>Constructs (overhangs)</u>
[11] <u>19</u> /308746 (S)	5'-AAGUAAGGACCAGAGACAAA-3'
[12] <u>20</u> /303912 (AS)	3'-UUCAUUCUGGUCUCUGUUU-P 5'
[12] <u>21</u> /316449 (AS)	3'- <u>UUCAUUCUGGUCUCUGUUU-P</u> 5'
[12] <u>36</u> /319013 (AS)	3'- <u>UUCAUUCUGGUCUCUGUUU-P</u> 5'
[12] <u>37</u> /319014 (AS)	3'- <u>UUCAUUCUGGUCUCUGUUU-P</u> 5'
[12] <u>38</u> /319015 (AS)	3'- <u>UUCAUUCUGGUCUCUGUUU-P</u> 5'

Please amend paragraph 313 on page 118 as shown below.

The following antisense strands of siRNA's were hybridized to the complementary full phosphodiester sense strand. Bolded monomers are 2'-OMe containing monomers. Underlined monomers have PS linkages. Monomers without underlines have PO linkages.

SEQ ID NO/ISIS NO

[16] 39/300852 5'-OH-CUG **CUA** GCC UCU GGA UUU **GA** (OMe/PO)
[16] 39/300853 5'-P- CUG **CUA** GCC UCU GGA UUU **GA** (OMe/PO)

[16] <u>40</u> /300854	5'-OH- CUG CUA GCC UCU GGA UUU GA	(OMe/PO)
[16] <u>41</u> /300855	5'-P- CUG CUA GCC UCU GGA UUU GA	(OMe/PO/PS)
[17] <u>42</u> /300856	5'OH- CUA GCC UCU GGA UUU GA	(OMe/PO/PS)
[16] <u>43</u> /300858	5'-OH- CUG CUA GCC UCU GGA UUU GA	(OMe/PS)
[16] <u>43</u> /300859	5'-P- CUG CUA GCC UCU GGA UUU GA	(OMe/PS)
[17] <u>44</u> /300860	5'-OH- CUA GCC UCU GGA UUU GA	(OMe/PS)
[18] <u>45</u> /303913	5'-OH- GUC UCU GGU CCU UAC UU	(OMe/PS)
[19] <u>46</u> /303915	5'-OH- UUU UGU CUC UGG UCC UU	(OMe/PS)
[20] <u>47</u> /303917	5'-OH- CUG GUC CUU ACU UCC CC	(OMe/PS)
[21] <u>48</u> /308743	5'P- UUU GUC UCU GGU CCU UAC UU	(OMe/PS)
[22] <u>49</u> /308744	5'-P- UCU CUG GUC CUU ACU UCC CC	(OMe/PS)
[23] <u>50</u> /328795	5'-P- UUU GUC UCU GGU CCU UAC UU	(OMe/PS)

Please amend paragraph 314 spanning pages 118-119 as follows.

The following antisense strands of siRNA's were hybridized to the complementary full phosphodiester sense strand. Where the antisense strand has a TT 3'-terminus the corresponding sense strand also has a 3'-TT (deoxyT's)

SEQ ID NO./ISIS NO.

[24] <u>51</u> /271065	CUG CUA GCC UCU GGA UUU GTT	PO
[25] <u>52</u> /271067	CUG CUA GCC UCU GGA UUU GUU	PO
[26] <u>53</u> /271069	CUG CUA GCC UCU GGA UUU GUT	PO
[24] <u>54</u> /271071	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>55</u> /271072	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>56</u> /271073	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>57</u> /271074	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>58</u> /271075	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>59</u> /271076	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>60</u> /271077	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>61</u> /271078	CUG CUA GCC UCU GGA UUU GTT	PO
[25] <u>62</u> /271079	CUG CUA GCC UCU GGA UUU GUU	PO

[26] <u>63</u> /271081	CUG CUA GCC TCT GGA TTT GUU	PO
[27] <u>64</u> /271082	CUG CUA GCC UCU GGA UUU GAC	PO/PS
[26] <u>65</u> /271083	CUG CUA GCC UCU GGA UUU GUU	PO/PS
[24] <u>66</u> /271084	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>67</u> /283547	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>68</u> /293999	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>69</u> /294000	CUG CUA GCC UCU GGA UUU GTT	PO
[24] <u>70</u> /290223	CUG CUA GCC UCU GGA UUU GTT	PO

Please amend paragraph 315 spanning pages 119-120 as shown below.

The following antisense strands of siRNA's were hybridized to the complementary full phosphodiester sense strand. Bolded monomers are 2'-F containing monomers. Underlined monomers have PS linkages. Monomers without underlines have PO linkages. Sense stands (S) are listed 3' -> 5'. Antisense strands (AS) are listed 5' -> 3'.

SEQ ID NO/ISIS NO		Seauence	Features
[28] <u>71</u> /279471	AS	"CUG "CUA G"C"CU U"CU GGA UUU G dTdT (F/PO)	
[29] <u>72</u> /279467	S	"CAA AU"C "CAG AGG "CUA G"CA G dTdT (F/PO)	
[30] <u>73</u> /319018	AS	UU UGU CUC UGG UCC UUA CUU	(F/PO)
[31] <u>74</u> /319019	S	AAG UAA GGA CCA GAG ACA AA	(F/PO)
[30] <u>75</u> /319022	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/PS)
[30] <u>76</u> /333749	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>77</u> /333750	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>77</u> /333751	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>78</u> /333752	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>79</u> /333753	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>80</u> /333754	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>81</u> /333756	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>82</u> /334253	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>83</u> /334254	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)

DOCKET NO.: ISIS-5326
Application No.: 10/700,930
Preliminary Amendment - First Action Not Yet Received

PATENT

[30] <u>84</u> /334255	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>85</u> /334256	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>86</u> /334257	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[30] <u>87</u> /317466	AS	<u>UUU GUC UCU GGU CCU UAC UU</u>	PS
[30] <u>88</u> /317468	AS	<u>UUU GUC UCU GGU CCU UAC UU</u>	PO
[30] <u>89</u> /317502	AS	<u>UUU GUC UCU GGU CCU UAC UU</u>	PS

Please amend paragraph 317 on page 121 as follows.

The following antisense strands of siRNA's were hybridized to the complementary full phosphodiester sense strand. Where the antisense strand has a TT 3'-terminus the corresponding sense strand also has a 3'-TT (deoxyT's). Bolded monomers are 2'-F containing monomers. Underlined monomers are 2'-OMe. Monomers that are not bolded or underlined do not contain a sugar surrogate. Linkages are shown in the parenthesis after the sequence.

SEQ ID NO./ ISIS NO.	Composition (5' 3')	Features
[32] <u>90</u> /283546	CUG CUA GCC UCU GGA <u>UUU GU</u> .dT-3'	(OMe/F/PO)
[33] <u>91</u> /336240	UUU GUC UCU GGU CCU UAC UU	(OMe/F/PS)

Please amend paragraph 318 spanning pages 121-122 as follows.

The following antisense strands of siRNA's were hybridized to the complementary full phosphodiester sense strand. Bolded monomers are 2'-OMOE. Linkages are phosphothioate.

SEQ ID NO	Composition	PTEN mRNA level (%UTC) 100 nM oligomer
[34] <u>92</u>	UUC AUU CCU GGU CUC UGU UU	--
[34] <u>93</u>	UUC AUU CCU GGU CUC UGU UU	50

[34] <u>94</u>	UUC AUU CCU GGU CUC UGU UU	--
[34] <u>95</u>	UUC AUU CCU GGU CUC UGU UU	43
[34] <u>96</u>	UUC AUU CCU GGU CUC UGU UU	42
[34] <u>97</u>	UUC AUU CCU GGU CUC UGU UU	47
[34] <u>98</u>	UUC AUU CCU GGU CUC UGU UU	63

Please amend paragraph 319 on page 122 as shown below.

Strands listed below can be made by methods of Example 22 and can be duplexed with the complementary strand. Monomers in bold are 4'-thioribonucleosides. Non-bolded monomers are ribonucleosides. Underlined monomers have phosphothioate linkages. Other linkages are phosphodiester.

SEQ ID NO. Sequence (5' 3')

[35] <u>99</u>	UUU GUC UCU GGU CCU UAC UU
[35] <u>100</u>	<u>UUU GUC</u> UCU GGU CCU UAC UU
[35] <u>101</u>	UUU GUC UCU GGU CCU UAC UU
[35] <u>102</u>	<u>UUU GUC</u> UCU GGU CCU UAC UU

Please amend paragraph 321 spanning pages 122-123 as shown below.

The antisense (AS) strands listed below were individually duplexed with the complementary RNA sense strand. Monomers in bold are 4'-thioribonucleosides (4'S). Oligomers with phosphothioate linkages are listed as PS. PO linkages are phosphodiester.

SEQ ID NO./ISIS NO.	Sequence (3' 5')	Linkage Sugar	
[36] <u>103</u> /303912	UUC AUU CCU GGU CUC UGU UU	PS	2'OH
[36] <u>104</u> /336675	UUC AUU CCU GGU CUC UGU UU	PO	4'S
[36] <u>105</u> /336671	UUC AUU CCU GGU CUC UGU UU	PO	4'S
[36] <u>106</u> /336674	UUC AUU CCU GGU CUC UGU UU	PO	4'S
[36] <u>107</u> /336672	UUC AUU CCU GGU CUC UGU UU	PO	4'S

DOCKET NO.: ISIS-5326
Application No.: 10/700,930
Preliminary Amendment - First Action Not Yet Received

PATENT

[36] <u>108</u> /336673	UUC AUU CCU GGU CUC UGU UU	PO	4'S
[36] <u>109</u> /336676	UUC AUU CCU GGU CUC UGU UU	PO	4'S
[36] <u>110</u> /336678	UUC AUU CCU GGU CUC UGU UU	PO	4'S

Please amend paragraph 323 spanning pages 123-124 as follows.

Strands listed below can be made by methods of Example 25 and can be duplexed with the complementary strand. Attached to each of the monomers identified with a "*" is 3'-abasic ribonucleosides. The remaining monomers are ribonucleosides. Underlined monomers have phosphothioate linkages. Other linkages are phosphodiester.

<u>SEQ ID NO.</u>	<u>Sequence (5' 3')</u>
[35] <u>111</u>	UUU GUC UCU GGU CCU UAC UU*
[35] <u>112</u>	UUU <u>GUC UCU GGU CCU</u> UAC UU*
[35] <u>113</u>	<u>UUU GUC UCU GGU CCU UAC</u> UU*